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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jeffrey A. Hubbell et al.	Art Unit:	1615
Serial No.:	09/559,984	Examiner:	L. Di Nola Baron
Filed:	April 26, 2000	Customer No.:	21559
Title:	IN SITU FORMING HYDROGELS		

Assistant Commissioner For Patents
Washington, DC 20231

REPLY TO EXAMINER'S ACTION

In reply to the Examiner's Action mailed October 9, 2001, Applicants make the following remarks.

The Office Action

Claims 1-18 are pending. Claims 1, 5, and 9 stand rejected for anticipation by Amiel et al. (J. Inclusion Phen. & Mol. Recog. 1996, 25:61-67; hereafter "Amiel"). Claims 1-18 stand rejected for obviousness over Amiel in view of Hedstrand et al. (U.S. Patent No. 5,560,929; hereafter "Hedstrand"), Rhee et al.

(U.S. Patent No. 5,324,775; hereafter "Rhee"), and Jodal et al. (Starch 1984, 36:140-143; hereafter "Jodal").

Rejections under 35 U.S.C. § 102(b)

Claims 1, 5, and 9 stand rejected for anticipation by Amiel. The Examiner states:

> Amiel et al. discloses hydrophobically end-capped polyethylene oxide and water-soluble β-cyclodextrin polymers... Said polymers meet the limitations of claims 1, 5, and 9 of the instant application, as they contemplate a hydrogel precursor comprising a polymer and a protecting group, specifically cyclodextrin.

Applicants disagree. The hydrogel of Amiel is formed by the interaction of the hydrophobic end-caps and the cavity of β-cyclodextrin. No hydrogel forms from the end-capped polymer without the β-cyclodextrin present. This composition is thus a two part system that forms a gel and is distinct from that of claim 1 (from which claims 5 and 9 depend), because the composition of claim 1 is a system having at least two parts that do not form a gel. Claim 1 is directed to polymers that form a hydrogel in the absence of a physical chemical protecting group (e.g., β-cyclodextrin) and further requires the addition of a protecting group, which prevents gel formation by the polymer. The potential presence of cyclodextrin or polymers containing hydrophobic groups in both compositions does not mean that the compositions are the same, as is clearly indicated in this case by the differences in the physical properties of the two compositions. In Amiel, the

composition forms a gel, but the composition of claim 1 cannot form a gel. In sum, the compositions of Amiel do not anticipate claim 1, and Applicants request that the rejection of claims 1, 5, and 9 be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1-18 stand rejected for obviousness over Amiel in view of Hedstrand, Rhee, and Jodal. The Examiner asserts that the invention as a whole would be *prima facie* obvious to one of skill in the art. The MPEP § 2142 states: "[t]o establish a *prima facie* case of obviousness,... the prior art reference (or references when combined) must teach or suggest all the claim limitations." The rejection of each independent claim is addressed below with reference to the cited prior art.

Claim 1, as stated above, is an entirely different composition than that taught by Amiel. Amiel fails to teach a hydrogel precursor composition or the use of a physical chemical protecting group to prevent gelation. The polymers of Hedstrand are dendritic polymers with hydrophobic end-caps. Hedstrand does not disclose the inclusion of a physical chemical protecting group that prevents gelation of these polymers. Rhee discloses polymers that have hydrophilic synthetic groups bound to naturally occurring groups. The polymers of Rhee form by the reaction of a suitably functionalized synthetic hydrophilic polymer with a suitably functionalized natural polymer, and Rhee is silent regarding the

prevention of gelation by a physical chemical protecting group. Indeed, since the polymers of Rhee form by a covalent reaction between synthetic and naturally occurring polymers, a physical chemical protecting group, even if one had been present (which it was not), would have been incapable of preventing gelation. Jodal discloses the degradation of cyclodextrin by α-amylase and is not relevant to claim 1. Hedstrand, Rhee, and Jodal do not remedy the deficiencies of Amiel since none of Hedstrand, Rhee, and Jodal teach a hydrogel precursor incorporating a physical chemical protecting group that prevents gel formation of a composition that would otherwise be in a hydrogel state.

Claim 2 is directed to the composition of claim 1 having in addition a molecule that disrupts the interactions between the polymer and the protecting group. This composition, unlike that of claim 1, is capable of forming a gel since the disruption of the interactions of the polymer and the protecting group allows the polymer to gel. The Examiner states:

> [I]t would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the hydrogel precursors disclosed by Amiel et al. or Rhee et al., by including a molecule, such as an α -amylase, to disrupt the interaction between the polymer and cyclodextrin.

As stated above, the hydrogels of Amiel and Rhee are not the same as the compositions of claim 1. As with Amiel, the polymers of Rhee may include cyclodextrin. Since cyclodextrin is a structural component of the polymers of Amiel and Rhee, the combination of Jodal and Amiel or Rhee would not be

capable of yielding a hydrogel, as recited in claim 2. The enzyme disclosed in Jodal would degrade the cyclodextrin in the compositions of Amiel and Rhee and cause the gels to disintegrate. The composition of claim 2 and the composition formed by the combination of Amiel, Rhee, and Jodal are thus not the same since the enzyme of Jodal would have an effect on the compositions of Amiel and Rhee that is the opposite of the effect that the enzyme would have on the composition of claim 2. Furthermore, since not one of Amiel, Rhee, or Jodal teaches the prevention of gelation, no combination of Amiel, Rhee, and Jodal teaches or suggests the inclusion of a molecule to disrupt the prevention of gelation as required by claim 2.

Claim 14 recites a method of forming a hydrogel in contact with a tissue using the composition of claim 2. As stated above, the combination of Amiel, Rhee, and Jodal does not teach or suggest the composition of claim 2. Thus, the combination of Amiel, Rhee, and Jodal does not teach or suggest the method of claim 14, which requires the composition of claim 2.

Regarding claims 15 and 16, the invention features methods for forming a hydrogel in contact with a tissue. In these cases, the polymers used in the methods are prevented from gelling by an organic solvent rather than by a physical chemical protecting group. The Examiner asserts that Rhee teaches a hydrogel that may be injected into a patient and that a carrier is then removed from the composition. Rhee states:

> One may administer the reaction mixture by injection before crosslinking has completed. In this embodiment, an aqueous collagen mixture is combined with a low-concentration of dPEG* solution, mixed, and the combination injected or applied before the viscosity increases sufficiently to render injection difficult. (Col. 29, lines 20-26)

The compositions of Rhee will thus eventually form a gel, even if initially in an injectable form and even if provided in a carrier. In the composition used in the method of claims 15 and 16, the carrier (i.e., organic solvent) prevents the polymers from gelling. The compositions used in the present methods are thus distinct from that of Rhee. In addition, none of Amiel, Rhee, Jodal, or Hedstrand teach or suggest a composition including an organic solvent that prevents polymers of the composition from gelling. Since none of the cited prior art references discloses the compositions required in claims 15 and 16, no combination of those references would yield the methods of claims 15 and 16.

Claims 17 and 18 relate to methods for incorporating sensitive biological materials into a hydrogel. While Rhee discloses the inclusion of biological materials, those compositions are not the same as those used in the methods of claims 17 and 18. The method of claim 17 uses the composition of claim 2, and the method of claim 18 uses the same composition as claims 15 and 16. As stated above, none of the prior art references teach or disclose any of the compositions of claims 2, 15, or 16, and thus the combined references do not teach or suggest the methods of claims 17 and 18.

Additionally, Rhee and Hedstrand are cited as teaching certain limitations recited in the dependent claims. As is stated above, the references, even in combination, do not teach or suggest all of the limitations of the independent claims. Since the limitations of the broadest claims are not taught, the limitations of the dependent claims are also not disclosed by the cited references.

In sum, no combination of Amiel, Rhee, Hedstrand, and Jodal yields any of the potentially hydrogel forming compositions required by claims 1-18, and Applicants request that the rejection of the claims for obviousness be withdrawn.

CONCLUSION

In light of the foregoing remarks, Applicants submit that the claims are now in condition for allowance and such action is respectfully requested. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Date: 10 December 2001

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